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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,391	03/26/2001	Minoru Fujimori	2001-0206A	7242

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	27

DATE MAILED: 08/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,391	FUJIMORI ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-25 and 27-32* is/are pending in the application.

4a) Of the above claim(s) *6,7,15,17,18,23,25 and 27* is/are withdrawn from consideration.

5)☒ Claim(s) *22* is/are allowed.

6)☒ Claim(s) *3-5,8-14,16,19-21,24 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 3-25 and 27-32 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/3/03 has been entered.

Applicants' traversal filed on 6/3/03 is acknowledged and considered.

The amended claims 14, 22, and 32 in the amendment filed on 5/8/03 have been considered and entered.

Election/Restrictions

This application contains claims 4b, 6, 7, 15, 17-18, 23, 25, 27 drawn to a non-elected invention or species without traverse in Paper No.13 filed on 2/6/02 or because of the amendment to the claims.

Claim Objections

Claim 3 is objected to because of the following informalities: the wording of the claim is grammatically incorrect and redundant, e.g., "method for delivering gene in a system for

delivering a DNA"; "transformed with a recombinant DNA having said DNA is used as a gene delivery vector"; "a bacterium selected from the group consisting of *Bifidobacterium adolescentis, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium thermophirum, and Bifidobacterium pseududolongum* wherein said bacterium belonging to the genus *Bifidobacterium*".

Claims 12-14, 16, 19, 20, 21, and 24 are objected to because of the following informalities: The claims depend on claims 6 and 7 and these claims are drawn to a non-elected invention.

Claims 16, 19, and 20 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are directed to a product and the claim from which they depend is directed to a method for delivering a gene in a system and not to a method of producing said product. None of claims 3-11 are directed to a bacterium. In addition, the phrase "comprising the bacterium as claims in any one of claims 3 to 11" in claim 16 fails to further limit the subject matter set forth in any one of claims 3 to 11.

Claim 21 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the

claim(s) in independent form. Claim 21 is directed using a bacterium belonging to the genus of Bifidobacterium, which is broader than the species listed in any one of claims 3 to 11.

Claim Rejections - 35 USC § 112

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5 and 8-14, 16, 19, 20, 21, 24, and 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, comprising administering a genetically modified bacterium to an individual with cancer, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises an expression vector comprising a DNA sequence coding for an anti-tumor protein, and does not reasonably provide enablement for a method for specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, wherein the genetically modified bacterium selected from the group consisting of *Bifidobacterium adolescentis, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium thermophirum, and Bifidobacterium pseudolongum*, which comprises a DNA sequence coding for a protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence

or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention is using a bacterium from the genus *Bifidobacterium* as a gene delivery vector comprising a gene used in a method of delivering the gene delivery vector to tumor tissues under anaerobic conditions.

The art of record for *Bifidobacterium* as exemplified by Yazawa et al. (Breast Cancer Research and Treatment, Vol. 66, pp. 165-170, 2001) teaches that:

> *Bifidobacterium* is non-pathogenic bacteria found in the intestine of human and some other mammalian animals. These organisms are believed to have health-promoting properties for their host, including increase of the immune response, inhibition of carcinogenesis, and protection of the host against viral infections. However, despite increasing attention to this bacterium in many fields, little is known about its genetic property (page 165).

Furthermore, the state of the art for transforming bacterium from the genus *Bifidobacterium* is highly unpredictable as exemplified by Argnani et al. (IDS, Microbiology, Vol. 142, pp. 109-114). Argnani teaches:

> Although electroporation technique has proven to be widely applicable to genetically transform bacterial strains, all Bifidobacterium so far examined have proved refractory to efficient and reproducible transformation (page 109).

Yazawa, whom teaches that, further supports this:

> To be able to exploit the potential of these organisms for cancer gene therapy, detailed knowledge is required about such basic biological phenomena as cellular metabolism, gene expression, protein secretion, and genetics. Yazawa further states that, studies on

Bifidobacterium at the molecular level are severely limited in the absence of an efficient transformation. Recently, Matsumura and colleagues developed a system for convenient and reproducible genetic transformation of B. longum (page 169).

The as-filed specification provides several working examples displaying the transformation of *Bifidobacterium longum* with a gene and the deliver of the genetically modified bacterium to tumor-bearing mice (pages 46-61). The delivery displayed that the bacterium specifically targeted the tumors (page 48). In addition, one example displays the production of a genetically modified bacterium comprising a cytosine deaminase (CD) gene and an example introducing the bacterium, which was specifically expressed only in tumor tissues under anaerobic conditions in tumor-bearing mice (pages 55-61).

In view of the as-filed specification and the art of record for using *Bifidobacterium* as a gene delivery vector, the claimed invention is only enabled for producing and using the *Bifidobacterium longum* comprising a gene for use in specifically delivering to tumor tissues under anaerobic conditions in a mammal because the as-filed specification and the art of record do not provide sufficient guidance for one skilled in the art to reasonably extrapolate from using *Bifidobacterium longum* to using the genus *Bifidobacterium* without an undue amount of experimentation. The art of record display that studies on Bifidobacterium at the molecular level are severely limited in the absence of an efficient transformation. Therefore, the state of the art is considered unpredictable and the as-filed specification does not provide sufficient guidance for one skilled in the art to make and/or use a representative number of bacterium from the genus *Bifidobacterium* as gene delivery vectors.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed bacterium from the genus *Bifidobacterium* other than the *Bifidobacterium longum* can be genetically modified and used as a gene delivery vector, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid delivery method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

Furthermore, with respect to claims 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 24, 28, 29, 30, 31, and 32 directed to treating a solid tumor or delivering a gene to tumor tissue under anaerobic conditions, the specification only provides sufficient guidance for treating a tumor in an individual with cancer. The breadth of the claimed methods encompasses targeting genetically modified *Bifidobacterium* to a solid tumor in any environment, including an individual with cancer and a solid tumor *in vitro*. The specification only teaches one skilled in the art how to use the method for targeting the bacteria to a tumor in an individual with cancer. The as-filed specification does not teach one skilled in the art how to use the claimed method wherein the tumor is not in an individual with cancer. The art of record is absent for using the claimed method on solid tumors *in vitro*. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

Furthermore, with respect to claims 3, 4, 5, 12, 13, 21, 16, 19, 20, 24, 28, and 29, the claims encompass a recombinant *Bifidobacterium* comprising a DNA not operably linked to a promoter. The specification provides sufficient guidance for one skilled in the art to make and

use a recombinant *Bifidobacterium longum* comprising a promoter operatively linked to a DNA encoding an anti-tumor protein. However, the specification fails to provide sufficient guidance or evidence for one skilled in the art to make and use a recombinant *Bifidobacterium longum*, comprising a promoter that is not operatively linked to any specific nucleotide sequence. The teachings in the specification are directed to using a promoter to express an anti-tumor gene product. The as-filed specification provides sufficient guidance or factual evidence for how to make and use *Bifidobacterium longum* comprising a promoter operatively linked to DNA to direct DNA expression, however the claims do not recite such a structural limitation. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

In addition, with respect to claims 3, 8, 9, 10, 11, 12, 13, 24, 28, 29, 30, and 31 directed to treating a solid tumor or delivering a genetically modified bacterium to tumor tissues under anaerobic conditions, the claimed method encompasses using a DNA encoding a protein with/without anti-tumor activity. The specification provides sufficient guidance or evidence for one skilled in the art to use a DNA encoding a protein with anti-tumor activity, but does not provide sufficient guidance for one skilled in art to reasonably correlate from using a protein with anti-tumor activity to the full scope of the claimed method encompassing using any protein without anti-tumor activity (e.g. Factor VIII, dystrophin, HIV, etc.). Thus, the claimed method is only enabled for using a DNA encoding a protein having anti-tumor activity and not for the full breadth of the claimed method.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably

enable the for a method for specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises an expression vector comprising a DNA sequence coding for a protein. Given that efficiently transfecting a representative number of *Bifidobacterium* was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to how to reasonably correlate efficiently transfecting *Bifidobacterium longum* to the other species of *Bifidobacterium* cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of transfecting *Bifidobacterium*.

Applicant's arguments filed 6/3/03 have been fully considered but they are not persuasive.

The argument is moot with respect to US Patents 4,519,913, 6,569,653, and 6,217,766 because the patents do not use the same methods and materials as contemplated in the claimed invention. It is not apparent how one skilled in the art how to reasonably extrapolate from a process for reducing the concentration of water soluble selenium ions in an aqueous solution in patent '913, process for producing ethanol in patent '653, or a sulfur-reducing bacterium in patent '766 to the claimed method. None of the patents cited in the argument teach one skilled in the art how to make and use the claimed embodiments.

In addition, Applicants' traversal is acknowledged and is not found persuasive for the following reasons: In view of the In re Wands Factors, the as-filed specification only provides sufficient guidance or evidence for a method for specifically delivering to tumor tissues under

anaerobic conditions in an individual with cancer a genetically modified bacterium, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises a DNA sequence coding for a protein. More specifically, in view of the art of record at the time of filing (transforming bacterium from the genus *Bifidobacterium* is highly unpredictable as exemplified by Argnani et al.), it would take one skilled in the art an undue amount of experimentation to practice the full scope of the claims. It is acknowledged that the bacteria listed in the claims are cited in the post-filing art as possible gene delivery vectors, however, in view of the art of record citing the problems with transfecting different species of the genus *Bifidobacterium*, the as-filed specification only provides sufficient guidance for one skilled in the art to genetically engineer *Bifidobacterium longum* and does not provide sufficient guidance or evidence for one skilled in the art to reasonably correlate making and using genetically modified *Bifidobacterium longum* to any other claimed species from the genus *Bifidobacterium*.

It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, with respect to the assertion that upon Li et al., Cancer Gene Therapy, 2003:10:105-1111 and the similarities of species of Bifidobacterium, one skilled in the art would have reasonable expectation that the other claimed species would be useful as a gene delivery vehicle.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.

In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of making and using the claimed species of *Bifidobacterium* (See Argnani), for those skilled in the art to experiment with the different species of claimed *Bifidobacterium* so as to provide a therapeutic method of gene therapy as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what protocols are required for successfully transfecting different species *Bifidobacterium*, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 16, 19, 20, 21, 24, 28, 29, 30, 31, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 21, 24, 28, 29, 30, 31, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: delivering a recombinant *Bifidobacterium* comprising a DNA encoding a protein to a tumor tissue under anaerobic condition to an individual with cancer.

The phrase "use of the method as in any one of claims 3 to 11" in claim 24 is vague as to how the method of claims 3 to 11 is used. Suggest amending claim 24 as follows: -- The method of any one of claims 3 to 11, wherein the tumor tissues are solid tumors --.

The phrase "is used as" in claims 3 and 14 is a relative term, which renders the claim indefinite. The phrase "is used as" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims do not define the metes and bounds of the phrase. The claims do not define the term "used" and what way the gene delivery vector is used.

Applicant's arguments with respect to claims 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 24, 28, 29, 30, 31, and 32 have been considered but are moot in view of the new ground(s) of rejection.

Claims 16, 19, and 20 recite the limitation "the bacterium as claimed in any one of claims 3 to 11". There is insufficient antecedent basis for this limitation in the claim. None of the claims are directed to a bacterium.

Applicant's arguments with respect to claims 16, 19, and 20 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 3, 8, 9, 12, 14, 16, 19, 21, 24, and 28-31 are rejected under 35 U.S.C. 102(a) as being anticipated by Yazawa et al (IDS, Cancer Gene Therapy, Vol. 7, pp. 269-274, March 2000). Yazawa teaches using a genetically engineered *Bifidobacterium longum* comprising an expression vector comprising a gene coding for spectomycin adenyltransferase in a method of delivering the bacterium to solid tumor tissues in a mouse (abstract and pages 269-271).

Applicant's arguments filed on 6/3/03 have been fully considered but they are not persuasive because the Declaration filed on 5/2/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the 102(a) rejection as anticipated by Yazawa et al. (claims 3, 8, and 9).

The Declaration only establishes that the Yazawa et al. article is a 102(a) reference. The Yazawa publication has a different inventive entity then the entity in the instant application

because the Yazawa's publication lists five of the seven inventors listed in the application. The Office assumes that all of the inventors, absence evidence to the contrary, are the inventors of the application. The Declaration has not provided evidence that the seven inventors reduce the invention to practice before the five inventors listed on the Yazawa publication.

Suggest submitting a Declaration that the seven inventors reduce the invention to practice before the five inventors listed on the Yazawa publication or submit evidence that the two other inventors did not invent the subject matter rejected under 102(a).

Claims 3, 4, 8, 9,12, 14, 16, 19, 21, 24, and 28-31 are rejected under 35 U.S.C. 102(a) as being anticipated by Babincova et al. (Life and Medical Sciences Online, http://www.itrust.de/lamso/lpext.dll.Infobase0?title0003.htm?fn=docu 8/7/2000, pp. 1-4). Babincova teaches introducing a gene encoding a luciferase into the genome of *Bifidobacterium longum* and using the genetically modified bacteria comprising the luciferase gene in a method of destroying neoplastic cells (page 3-4). Babincova further teaches that *Bifidobacterium longum* is a nonpathogenic bacterium that selectively grows in hypoxic regions of tumors after systemic application (abstract).

Applicant's arguments filed on 6/3/03 have been fully considered but they are not persuasive because the Declaration filed on 5/2/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the 102(a) rejection as anticipated by Babinocova (claims 3, 4, 8, and 9).

The Declaration only establishes that the Yazawa et al. article is a 102(a) reference. The Yazawa publication has a different inventive entity then the entity in the instant application

because the Yazawa's publication lists five of the seven inventors listed in the application. The Office assumes that all of the inventors, absence evidence to the contrary, are the inventors of the application. The Declaration has not provided evidence that the seven inventors reduce the invention to practice before the five inventors listed on the Yazawa publication.

Suggest submitting a Declaration that the seven inventors reduce the invention to practice before the five inventors listed on the Yazawa publication or submit evidence that the two other inventors did not invent the subject matter rejected under 102(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-5, 8, 9, 12, 14, 16, 19, 20, 21, 24, and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Babincova et al. (Life and Medical Sciences Online, http://www.itrust.de/lamso/lpext.dll.Infobase0?title0003.htm?fn=docu 8/7/2000, pp. 1-4) taken with Tagliabue et al. (WO 96/11277). Babincova teaches introducing an anti-tumor gene into the genome of *Bifidobacterium longum* and using the genetically modified bacteria comprising the gene in a method of destroying neoplastic cells (page 3-4). Babincova further teaches that *Bifidobacterium longum* is a nonpathogenic bacterium that selectively grows in hypoxic regions of tumors after systemic application (abstract). However, Babincova does not specifically teach introducing a DNA coding for an interleukin-2 protein into a *Bifidobacterium longum* and using the genetically modified bacterium in a method of delivering the DNA coding for the protein having an anti-tumor activity to tumor tissues under anaerobic conditions.

However, at the time the invention was made, Tagliabue teaches methods and compositions for delivery of therapeutic compounds to a mammal by administration of a recombinant bacterium to the animal, the bacterium encoding a therapeutic protein (abstract). Tagliabue further teaches that the bacterial microorganism can selected from several bacteria including *Bifidobacterium longum* (page 10, lines 5-10 and page 10, lines 12-20). In addition, Tagliabue teaches that the gene can code for a protein selected from the interleukin protein family including IL-2 (page 13-14).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Babincova in further view of Tagliabue, namely to produce a genetically modified *Bifidobacterium longum* comprising a nucleic acid sequence encoding a interleukin-2 (IL-2) protein for use in a method of delivering the genetically modified bacterium to tumor tissues under anaerobic conditions. One of ordinary skill in the art would have been motivated to introduce the gene encoding IL-2 into *Bifidobacterium longum* because the bacterium is a nonpathogenic anaerobic bacterium, which can selectively localize to solid tumors in a mammal after systemic application and IL-2 was well known to one of ordinary skill in the art for its anti-tumor activity.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed on 6/3/03 have been fully considered but they are not persuasive because the Declaration filed on 5/2/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the the 103(a) rejection for claims 3-5, 8,9, 12, 14, 16, 19, 21, 24, and 28-31 as being unpatentable over Babincova taken with Tagliabue.

The Declaration only establishes that the Yazawa et al. article is a 102(a) reference. The Yazawa publication has a different inventive entity then the entity in the instant application because the Yazawa's publication lists five of the seven inventors listed in the application. The Office assumes that all of the inventors, absence evidence to the contrary, are the inventors of the application. The Declaration has not provided evidence that the seven inventors reduce the invention to practice before the five inventors listed on the Yazawa publication.

Suggest submitting a Declaration that the seven inventors reduce the invention to practice before the five inventors listed on the Yazawa publication or submit evidence that the two other inventors did not invent the subject matter rejected under 103(a).

Conclusion

Claim 22 is in condition for allowance because the claim is free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635